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ALTERATION OF RESPIRATORY RESPONSE TO CHEMICAL STIMULI FOLLOWING SERIAL HYPERBARIC EXPOSURES

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Experiments have been performed to quantitate the respiratory responses to CO_2 inhalation and hypoxia of hyperbarically-naive subjects. The subjects were given a series of standard hyperbaric exposures and their respiratory responses determined after each exposure over a period of two months. The subjects were subsequently restricted from further hyperbaric exposure for a further three months and their respiratory responses were determined approximately every two weeks.

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SUMMARY

Experiments were performed to quantitate the respiratory responses to CO_2 inhalation and hypoxia of hyperbarically-naive subjects. Three subjects were given a series of standard hyperbaric exposures and their respiratory responses were determined after each exposure over a period of two months. The subjects were subsequently restricted from further hyperbaric exposure for a further three months and their respiratory responses were determined approximately every two weeks. Initial exposure to the hyperbaric environment produced an increase in the respiratory response to CO_2 inhalation and is explained as a stress reaction to a novel situation. Further hyperbaric exposures produced a decrease in the respiratory response to CO_2 inhalation in all subjects, the mean decrease being 23.3% after the last exposure. The decreased CO_2 response was accompanied by a decrease in the resting alveolar CO_2 pressure, consistent with the slow development of a mild metabolic acidemia. The responses to hypoxia were more variable but tended to show an increase of sensitivity as an adaptation to hyperbaric exposure. The time-course of the adaptation of the CO_2 response following these hyperbaric exposures is much longer than any adaptation previously reported. It is unlikely therefore to be brought about solely by an alteration in an acid-base state of the subjects, an alteration in the threshold values of the peripheral or central chemoreceptors or a change in the CO_2 stores of the body. It is suggested that the adaptation is mediated by an alteration in proprioceptive stimuli from the chest wall.

METHODS AND PROCEDURES

The subjects were male volunteers who were fully informed of the nature and purpose of the experiments but not of the composition of the gas mixtures they would be breathing or of the order of events in any particular experiment. Each subject was comfortably seated in a semi-reclining position with most of the apparatus beside or behind him, out of his field of vision. They were encouraged to relax and read and low back-ground music was played to somewhat mask extraneous auditory stimuli. Experiments were performed in the morning with the subjects in a fasting state in an attempt to minimize the circadian and metabolic effects on respiration.

Any combination of O_2, N_2, and CO_2 would be supplied via calibrated flowmeters (Air Products and Chemicals, Inc. type E29-150 mm), the combined gas flow being maintained at about 71 L/min. The output of the flowmeters was led via a manifold to a humidifier which was thermostatically maintained at a temperature which would provide the subject with moist, euthermic gas; in practice, this temperature was found to be 38°C with the total gas flow and length of tubing used and the ambient temperature in the laboratory. The gas flow was carried by nearly smooth bore plastic tubing to a T-piece (3 cm ID) within 10 cm of the inspiratory valve and the surplus gas blown off down a 3 m long tube of similar internal diameter.

The subject breathed through a mouthpiece attached to a valve which was made in our workshop and is a modification of the Oxford respiratory valve (6). The deadspace of the valve is 47 ml, and at a steady flow of 200 L/min of air, the pressure drop across the inspiratory flap is 0.5 cm H_2O and across the expiratory flap is also 0.5 cm H_2O.

Pulmonary ventilation was measured by passing the expired gas through a 10 liter capacity low-resistance dry gas meter (Parkinson Cowan, type CD4). The spindle of the meter was connected to a 360^{o} potentiometer (Beckman Helipot, model 5711) connected with a 9.0 V source to a pen recorder so that a single rotation of the potentiometer wiper showed as a double traverse of the pen, and individual expirations appeared as steps. The meter was checked for total capacity (10 L) against a calibrated Tissot spirometer and minor variations in recorded volume during a cycle of 10 L were corrected to true volume by a calibration chart constructed from the continuous recording obtained during passage of a constant air flow. The sample flow-rate of the gas analyzers was added to the recorded ventilation. Gas meter temperature was continuously measured by a Yellow Springs thermistor positioned centrally in the outlet gas flow and expired gas volumes were later converted to BTPS, assuming the gas to have been saturated at the recorded temperatures.

Steady-state end-tidal gas was collected from above the expiratory flap of the respiratory valve by a Rahn-Otis sampler, modified according to the method of Brismar, Hesser and Matell (3). While the values for P_{CO_2} and P_{O_2} obtained by this method may differ from true alveolar values by a variable amount, they will however be comparable with values obtained in other work by the end-tidal method. For convenience, they are therefore denoted in this paper as alveolar partial pressures (P_A). The sample flow rate was 150 L/min and the gas was passed through a drying tube (dead space about 0.5 ml) and analyzed for CO_2 by an infra-red analyzer (Godart Capnograph, type 146) and for O_2 by a paramagnetic oxygen analyzer (Beckman, type F).

Heart rate was obtained continuously from a modified ECG Lead I, with recording electrodes being placed in the mid-clavicular line over the left and right 3rd intercostal spaces and the reference electrode in the left mid-axillary line over the 10th intercostal space. The ECG and the output from the analyzers and the gas meter potentiometer were displayed on a multi-channel hot-stylus recorder (Hewlett-Packard, 7700).

Hyperbaric Exposures

Since the subjects had not previously been exposed to the hyperbaric environment, their first experience was a "Pressure and O_2 Tolerance Test" in accordance with the regulation included in the U.S. Navy Diving Manual (37). This consisted of pressurization in a compression chamber breathing air to a simulated depth of 33 m (108 ft) in about 4 minutes, remaining at that pressure for a further 4 minutes and then decompression to 18.3 m (60 ft) in about 45 seconds. At 18.3 m, the subjects breathed 100 percent oxygen at rest for 30 minutes. On completion, they returned to breathing air and were decompressed to normal atmospheric pressure over a period of about 5 minutes. All subjects completed the test without adverse symptoms.

Thereafter, the hyperbaric exposure utilized was a standard air dive to 20.1 m (66 ft) for 50 minutes (37). In our compression chamber the exposure consisted of compression to 20.1 m in about 4 minutes, a stop at this pressure of about 46 minutes (to a combined total of 50 minutes form leaving atmospheric pressure) and decompression to

atmospheric pressure in about 6 minutes, the subject breathing air throughout the procedure.

A total of 25 such exposures were performed by 4 subjects. One subject received only 2 exposures and then exercised his right as a volunteer to remove himself from the program. The other subjects received 8, 8, and 7 exposures.

One exposure resulted in symptoms which could be attributed to decompression sickness. Six minutes after the completion of the exposure, the subject reported a slight pain on the dorsal surface of his left forearm on arrival in the laboratory. He returned to wait by the compression chamber and after a further 10 minutes, the pain had lessened and had shifted to the ventral surface of the forearm, being localized to a finger-point area. No other signs or symptoms of decompression sickness could be elicited. The subject returned to the laboratory and the experiment was performed. There was no exacerbation of symptoms during the experiment, at the completion of which the pain had disappeared. This was determined by direct questioning as the subject had not noticed the disappearance and had forgotten the initial occurrence. The subject's behaviour during the experiment was in no way unusual and the results of the experiment do not appear compromised by the possible mild decompression sickness.

Experimental Procedure

Each subject had the ECG electrodes applied and was then seated in a dentist's chair which was carefully adjusted to provide a stress-free position which would enable the subject to remain perfectly at rest (apart from his arms) for the 90 minutes required for the experiment.

The respiratory responses of the subject to chemical stimuli were investigated by a modification of the "4-point determination" of Cunningham and Lloyd (5). A period of 20 minutes breathing air was allowed for the subject to reach a steady resting state, the mean of the values measured over the last 10 minutes of this period being taken as the resting values for alveolar oxygen (P_{A,O_2}), alveolar carbon dioxide (P_{A,CO_2}), expired ventilation ($\dot{V}_E$), respiratory frequency (f) and heart rate (Hr).

The inspired partial pressure of CO_2 (P_{I,CO_2}) was then increased over a period of 3 or 4 minutes to a value which was dependent on the CO_2 sensitivity of the subject. The P_{I,CO_2} was usually 40 torr and was sufficient to raise P_{A,CO_2} by about 15 torr and result in $\dot{V}_E$ of 40-50 L/min. Another period of about 20 minutes was allowed on this inspired gas mixture to regain the steady-state. The criterion for reaching the steady-state was that $\dot{V}_E$ should not vary by more than ±2 L/min over the last 5 minutes of the period, the mean of the measured parameters over the last 2 or 3 minutes being taken to represent the "first high CO_2" determination.

The oxygen partial pressure of the inspired gas mixture (P_{I,O_2}) was then altered to produce a P_{A,O_2} of between 62-65 torr, retaining the previous P_{I,CO_2}. This mixture was breathed for 5 or 6 minutes, the mean of the parameters over the last 2 minutes being taken for the "1st hypoxic" determination.

P_{I,O_2} was then further reduced to produce P_{A,O_2} of about 45 torr, retaining the previous P_{I,CO_2}. This mixture was again breathed for

5 or 6 minutes allowed, the mean values over the last 2 minutes being taken to represent the "second high CO_2" determination.

P_{I,CO_2} was then reduced by 5 torr/min to about 20 torr, resulting in a reduction of $\dot{V}_E$ to a minmum of 20 L/min. As $\dot{V}_E$ decreased, P_{I,O_2} was increased to maintain P_{A,O_2} at the mean level attained during the "high CO_2" determination. It normally took 5 minutes to reach a new steady-state and mean values were taken over the subequent 5 minutes to represent the "low CO_2" parameters.

$P_{I,\ CO_2}$ was then reduced to zero over 5 minutes and a final, air-breathing, steady-state determination of resting values was made over a 10 minute period.

The gas analyzers were fully calibrated against standard gases during the initial equilibration period at high CO_2 and again while waiting for the steady-state to be reached before the final resting values. Standard gases were also measured at intervals throughout the experiment to form a basis for the later correction of the indicated values.

Parameters describing the respiratory response were obtained by the methods of the Oxford group (5, 21, 23, 38).

The mean of the values of the "first high CO_2" and "second high CO_2" determinations was taken and compared to the value of the "low CO_2" determination. This allowed calculation of the slope of the CO_2 response line in L/min/torr P_{A,CO_2} at the mean P_{A,O_2} and was denoted as S_1. This line was plotted on a graph of $\dot{V}_E$ (ordinate) against P_{A,CO_2} (abscissa) and when extrapolated to zero $\dot{V}_E$ would cut the P_{A,CO_2}

axis at a value B. The CO_2 response could then be described as $\dot{V}_E = S_1 (P_{A,CO_2} - B)$.

The points obtained from the "first hypoxic" and "second hypoxic" determinations were plotted and joined by straight lines to parameter B. The slopes of these lines were calculated and denoted as S_2 and S_3 and represent the CO_2 response at the known values of P_{A,O_2}.

The obtained values of S_1, S_2, and S_3 were plotted against their P_{A,O_2} to depict the hyperbolic relation indicating the interaction between P_{A,CO_2} and hypoxia. This relation was defined by calculating the two asymptotes (C and D) and the area constant AD, where A was the amount by which P_{A,O_2} exceeded C at the point on the curve where the slope S was twice D. The relation could then be described by the equation:

$$S = D\ [1 + A/(P_{A,O_2} - C)]$$

The overall response to CO_2 and O_2 of the subject's ventilation in each experiment could then be described by combining the above equations.

$$\dot{V}_E = D\ [1 + A/(P_{A,O_2} - C)]\ (P_{A,CO_2} - B)$$

In this equation, parameter A can be considered as being related to the sensitivity to hypoxia, B is related to the acid-base state of the subject and the threshold values of the chemoreceptors, C is related to the value of P_{A,O_2} at which the hypoxic stimulus to respiration becomes maximal and D describes the sensitivity to CO_2 inhalation in the absence of hypoxia.

The units of the parameters are A, torr P_{A,O_2}; B, torr P_{A,CO_2}; C, torr P_{A,O_2}; and D, L/min/torr P_{A,CO_2}.

The derived parameters from the experiments are shown in Tables 1, 2, and 3 together with the value of S_1. The slope S_1 was obtained at a P_{A,O_2} of about 133 torr and nearly represents the response that would be determined in the subject breathing air. The partial results on the subject who removed himself from the experimental series are not included in this paper.

The responses of subject 2 (Table 2) following his initial pressure exposure could not be obtained because of instrument failure. Determinations of responses were not obtained on four other occasions following standard dive exposures because of unavoidable committments of either the subject or the investigator.

RESULTS

The initial "pressure and O_2 test" hyperbaric exposure was followed, in the two subjects in which it was measured, by an increase in D. A similar increase in parameter D has been seen in the presence of an infusion of nor-epinephrine and it is probable that the increase seen in these experiments was a stress reaction to the novel environment (8). Thereafter, the trend in all subjects was for a decrease in S_1 and D. The mean decrease in D after the last hyperbaric exposure was 23.3%, from 3.09 to 2.37 L/min/torr P_{A,CO_2}, while the decrease in S_1 was 14.6%, from 3.78 to 3.23 L/min/torr P_{A,CO_2} (Table 4).

Subject 1 had to interrupt his serial hyperbaric exposures after the fourth week because of an upper respiratory tract infection. At that time, the value of D had fallen from an initial mean of 3.29 to 1.93 L/min/torr P_{A,CO_2}, a decrease of 41.3% (Table 1). The dives were

resumed in the seventh week, at which time D had risen to 2.53 L/min/torr P_{A,CO_2}. Following subequent hyperbaric exposures, parameter D fell only slightly to 2.40 L/min/torr P_{A,CO_2}.

During the dive series, parameter A showed a mean increase from 27.9 to 40.0 torr P_{A,O_2} while C decreased its mean value from 37.2 to 23.3 torr P_{A,O_2} (Table 4).

During the subsequent "recovery" period when the subjects were restricted from further hyperbaric exposures, the expected return toward initial, pre-exposure values was seen over the first 3 weeks. Parameter D increased to 2.74 L/min/torr P_{A,CO_2}, a decrease of 11.3% from the predive value, while S_1 increased to 3.58 L/min/torr P_{A,CO_2}, a decrease of 5.3% from the predive value. Parameter A showed a comparable return towards initial value but parameter C did not change.

The greatest return towards initial values occurred in week 3 in subject 2 and in week 4 in subjects 1 and 3 but thereafter all subjects showed a repeated decrease in S_1 and D, an increase in A and a very small further decrease in C. After 13 weeks of "recovery," parameter D was still decreased 19.1% below the predive mean value and S_1 was 11.9% decreased.

Parameter B showed no significant change although the trend was similar in all subjects. The extent of change was most marked in subject 2 and least in subject 3. During the hyperbaric series there was a decrease in mean value from 36.4 to 34.9 torr P_{A,CO_2}, a return towards the inital value during the early "recovery" period and a subsequent further decrease at 13 weeks to 33.5 torr P_{A,CO_2} (Table 4). The resting P_{A,CO_2} values of the subjects also changed to a small extent in

the same sense as parameter B.

DISCUSSION

The respiratory response of awake man to inhalation of CO_2 and the interaction between the CO_2 response curve and hypoxia have been extensively studied at normal atmospheric pressure (21, 26, 38). The responses to hypercapnia and hypoxia have been shown to be affected by numerous factors which include alterations in acid-base state, deep body temperature, catecholamines, external resistance to respiratory flow, exercise and body position (1, 2, 5, 9).

The extent of any alteration of the response to CO_2 occurring in hyperbaric environments is still undecided. Decreased ventilatory response of divers to CO_2 inhalation in the laboratory setting has been reported by some investigators (16, 31, 35) while others have failed to demonstrate any significant change (11, 13, 26). Also, an apparent retention of CO_2 has been reported in some deep diving investigations (17, 18, 32, 33) while other dives have been notable for the absence of any raised alveolar CO_2 pressure (14, 27).

It has often been reported that there is an alteration in the breathing pattern of the subjects of hyperbaric experiments and of many experienced divers. Their respiration becomes slower, while tidal volume (V_T) increases to maintain a constant expired ventilation ($\dot{V}_E$) (12, 18, 29, 30, 36). This is commonly explained as being an alteration to produce the necessary $\dot{V}_E$ with minimum respiratory work or force under conditions of increased gas density (16).

It has also been shown however that the slope of the $\dot{V}_E/V_T$ relation is positively correlated with the non-hypoxic CO_2 sensitivity of the

subject, i.e., with the slope of the CO_2 response line at an alveolar O_2 pressure of 200 torr (15). The alteration noted in the breathing pattern of subjects under hyperbaric conditions will decrease the slope of the $\dot{V}_E/V_T$ relation and provides evidence of the probability of a decrease in CO_2 sensitivity of these people.

Evidence has been reported to show that the sensitivity to CO_2 inhalation and the sensitivity to hypoxia were positively correlated (28). It has also been shown, both in experimental subjects (38) and in patients (34), that a great reduction of hypoxic sensitivity occurs in conditons of metabolic alkalemia in which the sensitivity to CO_2 is also greatly reduced.

There is therefore evidence that the sensitivity to CO_2 is reduced in subjects under hyperbaric conditions and that this may be accompanied by a reduction in the sensitivity to hypoxia. If these reductions in sensitivity can be demonstrated, they will have a bearing on cases of sudden collapse underwater, the design of diving apparatus and the protocol for saturation diving.

The "four-point determination" method of obtaining respiratory responses to CO_2 inhalation and hypoxia has been extensively used and has been shown to give satisfactory information in steady-state experiments. Its advantage is a saving of experimental time and hence, a decrease in the likelihood of a change in other factors affecting respiration during the course of an investigation. A full investigation would entail the determination of $\dot{V}_E$ at a minimum of one "high CO_2" point and at one "low CO_2" point for each value of P_{A,O_2}, thus providing a

family of response curves each being identified by its own value of S and B. Cunningham and Lloyd showed that the response curves determined in this manner for different values of P_{A,O_2} tend to have a constant parameter B, provided that the "low CO_2" point has a $\dot{V}_E$ of more than 15 L/min (21). Variations in B were, in general, within the experimental error of the method, and the advantage in stability of the subject during the "four-point determinations" outweighed the possible disadvantage of loss of accuracy of the hypoxic response curves.

A constant parameter B implies that the threshold settings of the central medullary and the peripheral chemoreceptors have the same value. Later work (38) showed that this is not always the case and that in acute metabolic acidemia it is possible to produce separation of the thresholds, resulting in a CO_2 response curve having three distinct components of different slope. The greatest slope has a value comparable with the normal CO_2 response of the subject and the smallest slope is comparable with the "dogleg" slope of the subject which is presumed to be the residual sensitivity of the subject when P_{A,CO_2} is below the threshold of the chemoreceptors. The intermediate slope can be explained as a region in which P_{A,CO_2} is above the threshold of the peripheral chemoreceptors, and thus shows a lesser relation between $\dot{V}_E$ and P_{A,CO_2}, but below the threshold of the central chemoreceptors (20, 38). It was shown that the abrupt alteration between the intermediate and upper parts of the response curve could occur at a $\dot{V}_E$ as high as 20 L/min.

In a four-point determination of response parameters in the presence

of acute acid-base change, the "low CO_2" point could fall on the intermediate slope instead of the upper slope and thus give a falsely low recording of S_1, B and (by calculation) D. The appearance of an intermediate slope can explain some of the previously noticed variability in parameter B and also casts some doubt on CO_2 response curves obtained with "low CO_2" points when $\dot{V}_E$ is below 20 L/min.

In the current experiments, care was taken to ensure that the "low CO_2" point was obtained at a $\dot{V}_E$ of more than 20 L/min and it was usually associated with a V_E about 25 L/min. In some experiments, an extra determination of CO_2 response was made with $\dot{V}_E$ about 29 L/min to see whether this point differed markedly from the response line obtained with the "high CO_2" points and the "low CO_2" point at 25 L/min. There was no marked divergence of the 20 L/min "low CO_2" point and hence it is concluded that there was no appreciable intermediate component of the CO_2 response curve present in these experiments. It is possible that an intermediate slope did exist with its upper limit at more than 25 L/min but such a relation has only once been reported previously (38) and is unlikely to have occurred in this series of experiments.

The presence of an intermediate part of the CO_2 response curve has been reported and implicated in diving incidents. Morrison et al investigated the respiratory response to CO_2 inhalation of a naval diver who reported four incidents during dives to about 70 meters over a period of four years. During each incident he experienced 'erratic breathing' and a spinning sensation and on three of the occasions he lost consciousness, twice while at depth and once on surfacing. He

returned to consciousness quickly without any reported convulsions and was quite well after each dive apart from having a slight headache. His response to CO_2 inhalation, at a mean P_{A,O_2} 108.8 torr, produced a curve having two distinct components; the lower part had a value of B of 36 torr P_{A,CO_2} with a slope of 1.65 L/min/torr P_{A,CO_2} while the upper part had a B of 43.2 torr and a slope of 2.27 L/min/torr P_{A,CO_2}, the two parts joining at a P_{A,CO_2} of about 51 torr. The lower part of this curve is assumed to be the intermediate part of a three-component curve, the "dogleg" part not having been obtained.

Morrison et al believed that the response to CO_2 inhalation of this diver was much reduced below the normal value and gave further evidence in that the subject's P_{A,CO_2} reached 64.9 torr when exercising at a work load of 400 Kg.M/min in a hyperbaric chamber at a simulated depth of 30 meters. They assumed that carbon dioxide retention must be strongly suspected as being at least partially responsible for the incidents recorded, and recommended that the diver should not dive to depths in excess of 50 meters while breathing air or oxygen-nitrogen mixtures.

A similar investigation was performed on a civilian diver who reported a series of incidents over a two year period (25). His symptoms mainly consisted of headaches which were usually slight and cleared quickly after surfacing but which were occasionally severe and remained for the rest of the day. On two occasions he had lost awareness or consciousness during dives to 40 meters, these dives being the deepest he had ever attempted.

His respiratory response to CO_2 inhalation produced a one-component

curve having a value for B of 20.2 torr P_{A,CO_2} and a slope of 0.82 l/min/torr P_{A,CO_2}. This response is extremely low when compared to normal subjects and was considered to represent an intermediate CO_2 response slope. The subject was unfortunately unavailable for later investigation but was advised that he was unsuited to diving.

In the experiments reported here, the tendency for change in parameter B was a decrease during the period of serial hyperbaric exposures, a return towards predive values during the early recovery period and a second decrease during the late recovery period. This is in agreement with the results shown by Doell et al who investigated the respiratory responses of subjects acutely exposed to 4 ATA (10). There was no sign of the increase in parameter B which would be expected in metabolic alkalemia secondary to a primary respiratory acidemia and which has been reported by Schaefer in men during acclimatization to an increased P_{I,CO_2} and during prolonged exposure to the high pressure environment (30, 32, 33). It is therefore concluded that retention of CO_2 during hyperbaric exposure did not play a significant part in the alteration of CO_2 response in these experiments.

The decreases seen in the slopes of the air-breathing CO_2 response line (S_1) and the response line in the absence of hypoxia (D) in subjects 1 and 2 exceed the maximum variations previously determined over a period of several weeks in subjects who had not been exposed to the hyperbaric environment. The decreases in subject 3 are similar to those maximum variations (38). The means of the results show an adaptation to serial hyperbaric exposure by a decrease in CO_2 sensitivity. A similar decrease in

CO_2 sensitivity has been shown in the Ama of Japan (31, 35), in breath-hold diving (31), in men acutely exposed to 4 ATA (10) and in some SCUBA divers (12, 16, 18). Other studies have compared the responses of groups of divers against the responses of non-divers and have shown that divers tend to have a lower CO_2 sensitivity than non-divers. Froeb however could find no difference in response between divers and non-divers but does not state the extent of the diving activity of his subjects in the three months immediately preceeding the investigations. Sterk (36) also was unable to show any significant overall change in ventilatory response to CO_2 in a group of seven divers, although three of his subjects did show a slightly diminished response after a two-week period of intensive diving.

It appears likely therefore, that adaptation to the hyperbaric environment by a decrease in the respiratory response to CO_2 is to be expected in people exposed to the environment. Significant decreases are not apparent in all people and evidence in these experiments and in those of Sterk (36) would suggest that a greateer degree of adaptation would occur in subjects initially having a high CO_2 response than in those with low initial response.

Evidence about the possible adaptation of response to hypoxia in the hyperbaric environment is not so clear. At normal atmospheric pressure, evidence has been reported that sensitivity to CO_2 inhalation and to hypoxia are positively correlated (28). A reduction of sensitivity to hypoxia could therefore be expected in the presence of the reduction of sensitivity to CO_2 shown in these experiments. The sensitivity to hypoxia,

denoted by parameter A, showed great variability in all subjects but the mean values showed a tendency for an increase in sensitivity during the serial hyperbaric exposures, i.e., a negative correlation with CO_2 sensitivity. An increase in hypoxia sensitivity would however, have been expected in the presence of the mild metabolic acidemia which developed during the hyperbaric exposure period, indicated by the decrease in parameter B (20, 38).

However, Doell et al (10) examined the hypoxia sensitivity of six subjects at 1 ATA and 4 ATA. The experimental method and calculation of respiratory parameters used (4) was similar to that used in the experiments reported here except that they assumed a constant value for parameter C of 32 torr P_{A,O_2}, and their parameter 'A' is equal to DA in this paper. Two subjects showed no alteration of sensitivity to hypoxia at high values of P_{A,CO_2}.

The time-course of the adaptation of response to CO_2 inhalation was much longer than had been expected. The subject's respiratory parameters had not regained their initial values after three months without further hyperbaric exposure, although Schaefer (31) reported that respiratory adaptation in breath-hold diving had been lost after a three month lay-off period.

The mechanism by which adaptation of response to CO_2 inhalation occurs remains uncertain. The respiratory adaptation to the acidemia brought about by CO_2 has a half-time which is dependent on the magnitude of the imposed change in P_{A,CO_2} and can be measured in minutes (7). Inhalation of CO_2 will alter cerebrospinal fluid bicarbonate concentration and hence

affect the central medullary chemoreceptors, but Michel reported that these changes become considerable within 90 minutes (22). The respiratory changes associated with metabolic acidemia and alkalemia and resetting of the threshold values of the chemoreceptors appear complete within 6 days in relative acidemia and 4 days in relative alkalemia (38). It is unlikely responsible for the adaptation to the hyperbaric environment.

A more probable explanation is an alteration of the proprioceptive stimuli to respiration arising in the chest wall. It is well recognized that divers adopt an alteration in the normal breathing pattern, either as a method of conserving their breathing gas supply or in an unconscious attempt to reduce the work of breathing. The tendency is for a decrease in the frequency of respiration and an increase in tidal volume, accompanied by a post-inspiratory pause. Hey et al (15) have shown that there is a positive correlation between the natural frequency of respiration and the sensitivty to CO_2 inhalation in different subjects and it is possible that an imposed alteration in respiratory frequency will produce an alteration in sensitivity in the same subject. Lally et al (16) have produced evidence that the proprioceptive input to respiration in divers in that the neurogenic response to ventilation at the start of exercise is significantly reduced below that of sedentary subjects, although it is not known whether this is an adaptation or a process of natural selection.

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Table 1. Respiratory parameters of subject 1.

		S_1	A	B	C	D
Predive		4.61	48.2	37.2	42.7	3.33
Predive		4.26	29.6	36.5	40.7	3.25
Pressure and O_2 test		4.46	30.2	38.1	32.6	3.46
Dive	Week 1	3.98	40.8	36.6	30.0	2.50
Dive	Week 2	3.47	47.9	36.8	20.8	2.48
Dive	Week 3	3.53	37.5	38.0	34.3	2.56
Dive	Week 4	3.12	70.4	34.7	18.9	1.93
Dive	Week 7	3.70	47.7	38.9	29.4	2.53
Dive	Week 8	3.86	73.8	36.7	14.3	2.38
Dive	Week 9	-	-	-	-	-
Dive	Week 10	3.89	63.8	38.4	28.8	2.40
Recovery	Week 1	3.29	39.1	36.9	29.0	2.39
Recovery	Week 3	4.00	39.6	36.5	29.8	2.89
Recovery	Week 4	4.45	52.7	36.9	25.5	2.98
Recovery	Week 5	3.62	37.8	35.6	19.4	2.74
Recovery	Week 9	4.12	47.7	36.2	26.0	2.76
Recovery	Week 13	3.41	56.5	34.9	21.2	2.59

Units
S_1 L/min/torr P_{A,O_2}
A torr P_{A,O_2}
B torr P_{A,CO_2}
C torr P_{A,CO_2}
D torr L/min/torr P_{a,CO_2}

Table 2. Respiratory parameters of subject 2.

		S_1	A	B	C	D
Predive		3.55	21.7	37.1	70.4	3.22
Predive		3.00	15.3	36.8	36.4	2.85
Pressure and O_2 test		-	-	-	-	-
Dive	Week 1	3.22	102.0	37.0	3.9	1.80
Dive	Week 2	3.11	47.0	35.4	17.9	2.22
Dive	Week 3	2.62	13.6	33.5	40.7	2.02
Dive	Week 4	2.69	50.3	32.8	13.1	1.88
Dive	Week 5	2.35	31.9	32.1	11.5	1.65
Dive	Week 6	-	-	-	-	-
Dive	Week 7	2.92	16.7	33.4	25.9	2.02
Dive	Week 8	2.59	19.4	31.2	20.6	2.22
Recovery	Week 2	3.06	24.6	34.2	17.5	2.11
Recovery	Week 3	3.22	48.0	34.3	12.9	2.30
Recovery	Week 4	2.83	67.7	32.6	1.5	1.87
Recovery	Week 5	2.55	64.4	32.8	16.4	1.84
Recovery	Week 9	2.33	30.8	33.1	18.9	1.83
Recovery	Week 13	2.94	35.2	31.7	30.2	2.03

Table 3. Respiratory parameters of subject 3.

		S_1	A	B	C	D
Predive		3.71	26.2	34.9	16.2	2.95
Predive		3.58	26.2	35.8	16.9	2.93
Pressure and O_2 test		3.73	20.2	36.0	15.2	3.19
Dive	Week 1	3.26	20.5	34.4	18.2	2.77
Dive	Week 2	3.25	11.5	34.5	39.8	2.66
Dive	Week 3	3.50	33.1	35.6	9.2	2.76
Dive	Week 4	3.45	67.1	35.9	14.3	2.72
Dive	Week 5	-	-	-	-	-
Dive	Week 6	-	-	-	-	-
Dive	Week 7	3.21	36.8	35.2	20.4	2.50
Recovery	Week 2	3.61	23.1	34.6	17.9	2.74
Recovery	Week 3	3.52	16.6	36.2	27.6	3.04
Recovery	Week 4	3.81	18.9	34.8	21.0	3.26
Recovery	Week 5	3.33	25.2	34.3	28.8	2.66
Recovery	Week 9	3.39	32.8	34.8	14.6	2.37
Recovery	Week 13	3.64	32.2	34.0	17.3	2.87

Table 4. Mean respiratory parameters of all subjects.

		S_1	A	B	C	D
Before hyperbaric exposure	(n = 6)	3.78	27.9	36.4	37.2	3.09
After last dive	(n = 3)	3.23	40.0	34.9	23.3	2.37
After 3 weeks of recovery	(n = 3)	3.58	34.7	35.7	23.4	2.74
After 13 weeks of recovery	(n = 3)	3.33	41.3	33.5	22.9	2.50